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Screening for obstructive sleep apnea in children with syndromic cleft lip and/or palate☆

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Summary *Background:* Craniofacial malformations including cleft lip and/or palate (CL/P) increase risk for obstructive sleep apnea (OSA). While 30% of CL/P occurs in the context of underlying genetic syndromes, few studies have investigated the prevalence of OSA in this high-risk group. This study aims to determine the incidence and risk factors of positive screening for OSA in this complex patient population.
Methods: The Pediatric Sleep Questionnaire (PSQ) was prospectively administered to all patients cared for by the cleft lip and palate clinic at the Children's Hospital of Philadelphia between January 2011 and August 2013. The PSQ is a 22-item, validated screening tool for OSA with a sensitivity and specificity of 0.83 and 0.87 in detecting an apnea-hypopnea index (AHI) >5/hour in healthy children. The Fisher exact and Chi-square tests were used for purposes of comparison.
Results: 178 patients with syndromic CL/P completed the PSQ. Mean cohort age was 8.1 ± 4.4 years. Patients were predominately female (53.9%), Caucasian (78.1%), and had Veau Class II cleft (50.6%). Craniofacial syndromes included isolated Pierre Robin Sequence (PRS) (29.8%), 22q11.2 deletion syndrome (14.6%), Van der Woude syndrome (6.7%), and other rare genetic abnormalities (28.8%). The overall incidence of positive OSA screening was 32.0%. Males were at increased risk for positive OSA screening ($P = 0.030$), as were non-Caucasians ($P = 0.044$). Symptoms with the highest positive predictive value for OSA were "others comment on child appearing sleepy" (76.2%) and "stops breathing during the night" (75.0%). Notably, patients with 22q11.2 deletion syndrome were at highest risk for positive screens (50.0%, $P = 0.042$).

☆ **Institutional Review Board**: This study was reviewed and approved by the Institutional Review Board of the Children's Hospital of Philadelphia.

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Conclusions: Nearly a third of our patients with syndromic CL/P screened positively for OSA (32.0%), highlighting the importance of screening in this at-risk population. Future work will correlate screening results with polysomnograms to help validate these findings.
Clinical question/level of evidence: Diagnostic, III.

Introduction

Orofacial clefts are the most common congenital defects of the head and neck, with an incidence of 1 in 680 live births each year.[1] Attention is often directed toward surgical repair of obvious deformities to maximize form and function, but recent efforts have addressed symptoms of upper airway obstruction in this at-risk group. Clinical signs of pediatric obstructive sleep apnea (OSA) are abnormal sleep arousals and oxyhemoglobin desaturations, but these are often undetected, and instead present as problems with learning, attention, and behavior.[2] The long-term sequelae of untreated OSA include failure to thrive, cardiorespiratory compromise, and even death.[3]

In syndromic patients, OSA is often multifactorial due to intrinsic abnormalities in the naso-pharyngeal and oropharyngeal anatomy, or resulting from surgical intervention. Children with CL/P can have maxillary or mandibular hypoplasia, macroglossia, or poor motor tone, and these can place patients at high-risk for OSA.[4,5] Roughly a third of all CL/P has an underlying genetic syndrome[6] and recent literature has described a greater risk for OSA in this complex group of patients.[7] Thus, considering these patients together with their non-syndromic counterparts may convey an inaccurate view of OSA risk. Furthermore, their physiologic, anatomic, and etiologic heterogeneity for OSA may make diagnosis and treatment more difficult.[8] Thus, it may be useful to categorize orofacial clefts as either syndromic or non-syndromic for the purposes of OSA diagnosis.

The American Academy of Pediatrics recommends objective testing via nocturnal polysomnography (PSG) to confirm the diagnosis of OSA.[9] In clinical practice however, only a small percentage of children with suspected OSA actually undergo PSG, and OSA diagnoses are often made clinically.[10] Issues of cost and access to care thwart the clinical utility of this tool, and thus an active area of investigation is the development of screening tools. The Pediatric Sleep Questionnaire (PSQ) is a 22-item, parent completed survey that asks questions related to disordered breathing, somnolence, and inattentiveness. This tool was validated with a sensitivity of 0.83 and specificity of 0.87 in detecting OSA among healthy children,[11] and is among the best available screening tools for pediatric OSA.[12]

Previous studies of OSA in children with syndromic CL/P are limited by small cohorts and highly heterogenous patient populations. We therefore performed a prospective administration of the PSQ to assess the incidence of positive OSA screening in a large sample of children with syndromic CL/P. Additionally, we sought to characterize clinical and demographic variables that increase the risk for positive OSA screening.

Methods

An IRB approved retrospective chart review was performed on consecutive patients seen in the cleft lip and palate clinic at the Children's Hospital of Philadelphia between January 2011 and August 2013. A paper copy of the Chervin Pediatric Sleep Questionnaire (PSQ) was prospectively administered to all patients and families. The PSQ consists of 22 "Yes/No" questions addressing symptoms of disordered breathing, day-time sleepiness, and behavioral disorders. A positive screen was obtained when the ratio of positive to total responses was $\geq$0.33. This cutoff was shown to detect an apnea-hypopnea index (AHI) of $>$5/hour in otherwise healthy children.[11]

A chart review was performed on all patients who completed the PSQ to obtain demographic information, clinical diagnoses, and surgical history. Demographic variables included age at time of screening, gender, body mass index percentile (BMI%), and race. BMI% was obtained via normalization to age matched control data from the Centers for Disease Control (CDC). BMI% values were only utilized if obtained within three months of PSQ administration. Race was reported as Caucasian, African American, Hispanic, or Asian. All children with non-syndromic CL/P were excluded from this study.

Clefts were classified according to the Veau Classification: cleft of the soft palate only (Veau I), cleft of the soft and hard palate (Veau II), unilateral complete cleft lip and palate (Veau III), and bilateral complete cleft lip and palate (Veau IV). Additionally, diagnoses of submucosal cleft palate (SMCP) and isolated cleft lip (CL) were recorded. Fisher's exact and Pearson's chi-squared tests were utilized where appropriate for purposes of comparison. Statistical calculations were conducted on STATA 13 (StataCorp, College Station, TX). *P* values less than 0.05 were deemed significant.

Results

178 patients met inclusion criteria and completed the PSQ questionnaire. Cohort descriptors are presented in Table 1. The mean age at OSA screening was 8.1 $\pm$ 4.4 years (range, 2—18 years). Patients were predominately female (53.9%), Caucasian (78.1%), and had Veau Class II clefts (50.6%). Pierre Robin Sequence (PRS) was the most prevalent craniofacial disorder, and was either isolated (29.8%),

Table 1 Cohort descriptors at time of Pediatric Sleep Questionnaire (PSQ) administration.

Patient characteristic	*N* (%)
Total	178 (100)
Age (years)	
2–4	54 (30.3)
5–9	70 (39.3)
10–13	30 (16.9)
14–18	24 (13.5)
Gender	
Male	82 (46.1)
Female	96 (53.9)
Ethnicity	
Caucasian	139 (78.1)
African American	17 (9.6)
Hispanic	13 (7.3)
Asian	9 (5.0)
Cleft type	
Cleft lip	2 (1.1)
Submucous cleft palate	31 (17.4)
Veau I	27 (15.2)
Veau II	90 (50.6)
Veau III	13 (7.3)
Veau IV	15 (8.4)
Syndrome	
Pierre Robin Sequence (PRS)	53 (29.8)
22q 11.2 deletion	26 (14.6)
Van der Woude	12 (6.7)
PRS + Stickler	10 (5.6)
PRS + other genetic disorder	8 (4.5)
Goldenhar	6 (3.4)
Apert	4 (2.2)
CHARGE	4 (2.2)
Treacher Collins	4 (2.2)
Other	51 (28.8)

Table 2 Summary of clinical factors associated with positive obstructive sleep apnea (OSA) screening.

Variable	No. patients with +OSA screening (%)	*P* value	X^2
Age (years)		0.412	2.87
2–4	14 (25.9)		
5–9	27 (38.6)		
10–13	10 (33.3)		
14–18	6 (25.0)		
Gender		0.030	4.72
Male	33 (40.2)		
Female	24 (25.0)		
Ethnicity		0.044	4.05
Caucasian	37 (26.2)		
Non-Caucasian	16 (43.2)		
BMI %		0.225	1.47
0–49.9	28 (26.7)		
50.0–100	25 (35.2)		
Cleft type		0.124	7.23
Cleft lip	0		
Submucous cleft palate	8 (25.8)		
Veau I	14 (51.9)		
Veau II	29 (32.2)		
Veau III	2 (15.4)		
Veau IV	4 (26.7)		
Syndrome		0.042	6.32
Pierre Robin Sequence (PRS)	14 (26.4)		
22q 11.2 deletion	13 (50.0)		
Other	26 (35.6)		

associated with Stickler syndrome (5.6%), or other genetic disorder (4.5%). 22q11.2 deletion syndrome was also prevalent (14.6%), followed by Goldenhar (3.4%), Apert (2.2%), CHARGE (2.2%), and Treacher Collins (2.2%) syndromes. A significant group had other rare genetic abnormalities commonly associated with CL/P (28.8%), including Kabuki, Ectrodactyly-ectodermal dysplasia-cleft (EEC), and Beck-with–Wiedemann syndromes.

32.0% of our patients screened positively for OSA. Table 2 summarizes the univariate analyses of clinical and demographic variables for positive OSA screening. Age at screening did not correlate with increased risk for OSA ($P = 0.412$). Interestingly, obesity measured via BMI% did not correlate with OSA risk ($P = 0.225$). Of significance, males demonstrated greater positive OSA screens (40.2% vs 25.0%, Figure 1, $P = 0.030$) as did non-Caucasians (43.2% vs 26.2%, Figure 2, $P = 0.030$). There was no significant association between cleft type and positive OSA screening (Figure 3, $P = 0.124$). Notably, 50.0% of patients with 22q 11.2 deletion syndrome had positive screens and were at the highest risk for OSA (Figure 4, $P = 0.042$).

Individual symptoms on the PSQ were analyzed for prevalence in the entire cohort, among positive screeners, and for positive predictive value (PPV, Table 3). The most commonly reported symptoms in the entire cohort were "mouth breather during the day" (44.4%) and "easily distracted" (41.6%). Among positive screeners the commonest symptoms were "easily distracted" (78.9%), "mouth breather during the day" (70.2%), "difficulty organizing tasks" (68.4%), and "fidgets with hands or feet" (68.4%). However, questions with the highest PPV for positive OSA

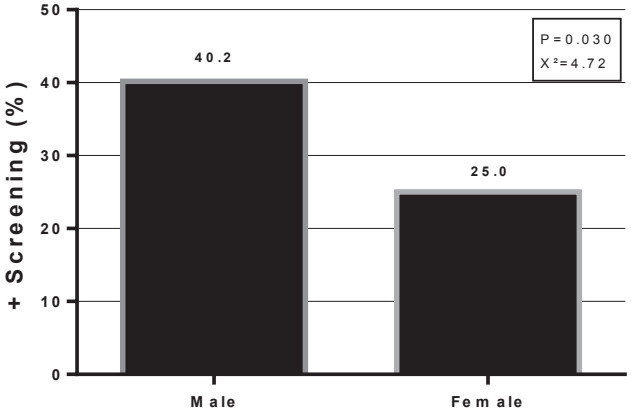

Figure 1 Gender and positive OSA screening.

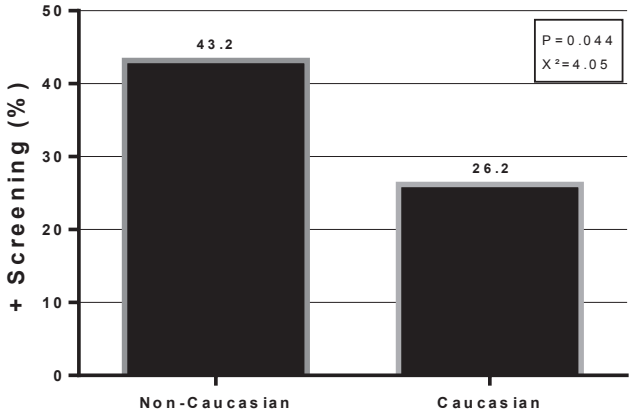

Figure 2 Race and positive OSA screening.

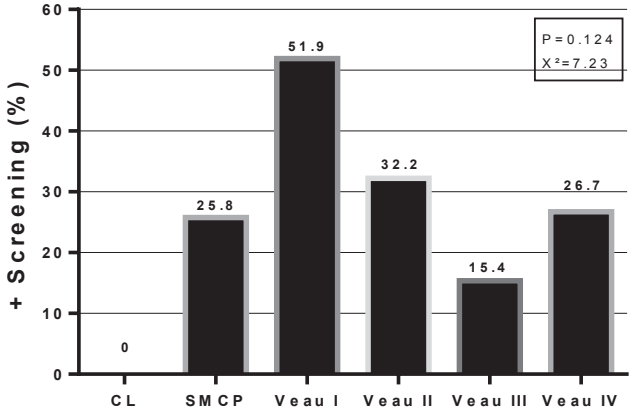

Figure 3 Cleft classification and positive OSA screening.

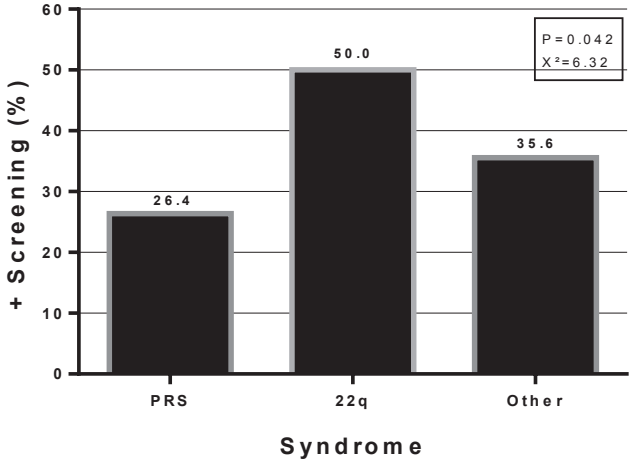

Figure 4 Craniofacial diagnoses and positive OSA screening.

screening were "others comment on child appearing sleepy" (76.2%) and "stops breathing during the night" (75.0%).

Table 4 displays positive OSA screening by craniofacial diagnosis. Due to limited sample sizes, statistical analyses could not be generated for rare craniofacial syndromes. However, 22q 11.2 deletion syndrome demonstrated the highest prevalence of positive OSA screening in the patient cohort (50.0%, Figure 4).

Discussion

Our study utilized prospective administration of the Pediatric Sleep Questionnaire (PSQ) to assess the prevalence of positive OSA screening in a large cohort of children with syndromic CL/P. Nearly a third of our patients screened positively for OSA (32.0%) and many displayed symptoms of sleep disordered breathing (Table 3). Thus, relative to the general pediatric population, children with syndromic CL/P may be up to 15 times more likely to develop OSA symptoms.[13,14] These findings are consistent with under-recognition of OSA in children with non-syndromic CL/P,[7,15] and highlight the importance of routine screening to help prevent the morbidity associated with OSA including adverse cardiorespiratory, neurodevelopmental, and behavioral consequences.[2]

Previous studies investigating OSA in children with orofacial clefts are limited to heterogeneous cohorts of craniofacial patients and specific surgical case series. This study is the first to report the incidence of positive OSA screening in a large cohort of children with syndromic CL/P. Our findings have implications for both surgical and anesthesia teams, as these patients often undergo a large number of procedures and exhibit complex upper airway anatomy.

Our results showed a higher prevalence of OSA screening in male patients with syndromic CL/P (40.2% vs 25.0%, $P = 0.030$, Figure 1). This finding is supported by epidemiological studies in the literature describing a classic male predominance for OSA.[16] Interestingly however, recent large studies failed to detect significant differences in OSA prevalence by sex.[17,18] In light of these contradicting data, it must be emphasized that children with craniofacial disorders often have different etiologies for upper airway obstruction relative to their non-affected peers. Thus, findings in the general pediatric literature do not always apply to children with CL/P. However, a common finding in the general pediatric literature upheld in our study was increased OSA disease burden for non-Caucasian children.[2] Our results showed an increased risk for positive OSA screening among non-Caucasian children (43.2% vs 26.2%, $P = 0.044$).

The Pediatric Sleep Questionnaire (PSQ) was designed and validated for the general pediatric population, of which obesity is a well-established risk factor for both pediatric and adult-onset OSA.[19] Our results show no correlation between BMI% and positive OSA screening ($P = 0.225$, Table 2). As a proxy for obesity, we expected patients with higher BMI% would be at increased risk for positive OSA screening. However, these findings could be due to sampling error, or it may speak to the distinct phenotypes and pathologic etiologies for OSA in our study cohort.

A growing body of literature endorses proactive OSA screening in children with syndromic craniofacial disorders. Among children under two years of age, MacLean et al. found an increased risk for questionnaire-diagnosed OSA in children with syndromic cleft palate.[20] Over three decades ago, Schafer described midface hypoplasia and collapsed airways in children with craniofacial anomalies that may

Table 3 Prevalence of individual obstructive sleep apnea (OSA) symptoms in patients with syndromic cleft lip and/or palate(CL/P).

Symptoms	Prevalence (%) among all patients	Prevalence (%) among positive screeners	Positive predictive value (%)
Snores more than half the time	29.8	54.4	35.2
Always snores	14.0	29.8	43.6
Snores loudly	25.8	45.6	50.0
"Heavy" or loud breathing during sleep	32.6	64.9	36.3
Trouble breathing during sleep	9.0	21.1	66.7
Stops breathing during the night	9.6	21.1	**75.0**
Mouth breather during the day	44.4	70.2	31.0
Wakes in the morning with a dry mouth	33.1	61.4	37.2
Occasionally wets the bed	25.3	42.1	25.3
Wakes up feeling unrefreshed	24.2	54.4	44.9
Problem with sleepiness during the day	16.9	40.4	46.0
Others comment on child appearing sleepy	9.0	28.1	**76.2**
Hard to wake in the morning	18.5	36.8	32.8
Wakes in the morning with a headache	5.1	8.8	41.7
Ever stopped growing at a normal rate	16.9	35.1	69.0
Overweight	3.9	8.8	33.3
Does not seem to listen when spoken to directly	23.0	54.4	46.3
Difficulty organizing tasks	31.5	68.4	62.9
Easily distracted	41.6	78.9	42.5
Fidgets with hands or feet	34.3	68.4	35.1
"On the go" or "driven by a motor"	27.0	50.9	28.7
Interrupts others	35.4	66.7	31.9

Bold represents the highest positive predictor values.

increase OSA risk.[21] Roughly half of all children with syndromic craniosynostoses, such as Crouzon, Apert, and Pfeiffer syndrome, develop OSA within the first six years of life.[22] In these patients, Pijpers et al. demonstrated questionnaire screening increases OSA detection over two-fold compared to clinical suspicion.[23] Thus, routine clinical screening may be warranted in this high-risk group of patients especially considering that parents of children with craniosynostosis may underestimate OSA symptoms.[24] Additionally, children with syndromic craniofacial dysostoses, including Treacher-Collins and Goldenhar syndrome, display a high incidence of upper airway obstruction.[25] Thus, it seems plausible that OSA contributes to the overall morbidity of children with syndromic craniofacial disorders.

Table 4 Craniofacial syndrome and prevalence of positive obstructive sleep apnea (OSA) screening.

Syndrome	No. of patients	No. of positive screeners (%)
Pierre Robin Sequence (PRS)	53	14 (26.4)
22q 11.2 deletion	26	13 (50.0)
Van Der Woude	12	0
PRS + Stickler	10	2 (20.0)
PRS + other syndrome	8	3 (37.5)
Goldenhar	6	2 (33.3)
Apert	4	1 (25.0)
CHARGE	4	1 (25.0)
Treacher Collins	4	3 (75.0)

22q11.2 deletion syndrome affects approximately 1 in 4000 births.[26] Patients with 22q display wide phenotypic variability, but have characteristic craniofacial morphologies including anatomic abnormalities of the palate, neuromuscular pathologies of the oropharynx, and retrognathia.[27] These children commonly undergo multiple upper airway surgeries, and may be predisposed to develop OSA symptoms. As such, parents of children with 22q may harbor heightened vigilance for symptoms of sleep-disordered breathing. Our results showed the highest risk for positive OSA screening in patients with 22q (50.0%, Figure 4). The true incidence of OSA in patients with 22q is unknown and its impact is likely underappreciated. Our findings warrant additional study in this high-risk group to assess the true prevalence of OSA by polysomnogram (PSG), and to assess factors predisposing children with 22q to OSA.

A limitation of the present study is the questionnaire nature of the screening tool we employed to determine the prevalence of OSA symptoms. While PSG has many advantages, including its ability to distinguish between central and obstructive sleep apneas, access-to-care issues commonly limit its clinical utility. Despite this, PSG remains the gold standard for diagnostic purposes, but has never been validated to predict adverse clinical sequelae or response to medical treatment.[28] Thus, even in the presence of PSG confirmation, OSA symptoms can still result in adverse neurocognitive and behavioral consequences. Furthermore, in cases where OSA is well-documented clinically, PSG may not be absolutely indicated.[2] Given these limitations, the development of alternative screening tools for OSA is an active area of research.

The Chervin PSQ is among the best screening tools for pediatric OSA with a reported sensitivity and specificity of 83% and 87% for detecting an AHI >5.0 in children 2—18 years of age.[11] Until better tools are developed, PSG and questionnaires based on its reliability must be used in the diagnosis and treatment of OSA. The authors acknowledge a notable limitation of applying the PSQ to this patient population is that the parent's of children with craniofacial syndromes including clefts may be sensitized to airway issues and, thus, over report symptoms. Secondly, patient families occasionally omitted PSQ questions that did not pertain to their child. For example, although validated in a wide age group, the PSQ contains questions such as "occasionally wets the bed" which may limit its applicability to children wearing diapers. These omissions may compromise the utility of this screening tool, and is a limitation of paper administration of the PSQ. Ultimately, the PSQ will require additional studies to validate its application to this patient population. Lastly, we utilized retrospective chart review to assess the impact of clinical variables on positive OSA screening. This methodology is limited through sampling bias, transfer of care issues, and differential follow-up. Thus, we cannot make strong conclusions regarding PSQ correlations with clinical variables.

Conclusion

Nearly a third of our patients with syndromic CL/P screened positively for OSA (32.0%), highlighting the importance of screening in this at-risk population. Future work will correlate screening results with polysomnograms to determine the true incidence of OSA in syndromic CL/P.

Conflict of interest

None.

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